New regression models for long-term cognitive change in Donepezil treated Alzheimer patients

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Conclusions
There is considerable heterogeneity in the raw observations of the rate of change. Analyses of the rates of progression in donepezil treated patients showed that the rate of change of ADAS-cog and MMSE scores depends strongly on the current score for the time interval examined. The measured rate of change indicated more rapid improvement for the more severely affected patients. Both quadratic and cubic functions adequately characterize progression of Alzheimer’s disease. However, the regression models showed a slower cognitive deterioration in donepezil treated patients compared to earlier studies of untreated patients.

Introduction
The Swedish Alzheimer Treatment Study (SATS) was started in order to describe the long-term effects of cholinesterase inhibitor treatment in patients with Alzheimer’s Disease (AD) in a routine clinical setting. Donepezil was the first of the second-generation inhibitors of acetylcholinesterase (ChEi) to get approval in Sweden 1997. Since placebo controlled long term studies in AD treatment are no longer considered ethical, the problem with non-treated groups for comparison exists. Whether it would be feasible for future assessment of new drugs for AD treatment without placebo groups to compare them with ChEi.

Methods and Subjects
SATS is a descriptive, prospective, longitudinal, multicentre study. 435 outpatients with the clinical diagnosis of AD received treatment with donepezil for a period of three years. Among the primary efficacy parameters assessed were MMSE and ADAS cognitive subscale. Patients were assessed at baseline, at 2 months (not ADAS-cog) and every 6 months during the study.

To simplify comparisons, change of score in this paper is calculated so that all positive values indicate improvement and all negative values indicate worsening. We computed the difference between baseline i.e. start of donepezil treatment and the 6 months score and then calculated mean ± SD.

Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Untreated patients (2-4 points decline/year)</th>
<th>Untreated patients (6 observations below baseline score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>33% (65%)</td>
<td>35% (70%)</td>
</tr>
<tr>
<td>Age at investigation, mean ± SD (range)</td>
<td>74.7 ± 6.5 (50 - 87)</td>
<td>74.7 ± 6.5 (50 - 87)</td>
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<tr>
<td>Duration, years ± SD</td>
<td>3.1 ± 2.3</td>
<td>3.1 ± 2.3</td>
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<tr>
<td>MMSE, mean ± SD, (range)</td>
<td>22.0 ± 4.6 (30 - 6)</td>
<td>22.0 ± 4.6 (30 - 6)</td>
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<tr>
<td>ADAS-cog (0-70), mean ± SD, (range)</td>
<td>20.7 ± 10.0 (3 - 99)</td>
<td>20.7 ± 10.0 (3 - 99)</td>
</tr>
</tbody>
</table>

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Objective
To calculate regression models, which show the development of cognitive function in donepezil treated patients. In addition, to analyse how the patients’ baseline scores have an impact on the change in cognition after 6 months of treatment.

Results
There was a significant quadratic and cubic component between baseline scores on ADAS cog or MMSE versus 6 months mean cognitive change. Linear and several nonlinear models were also tested but these models were not significant. Here we present the cubic models which have most of the variation explained by the model, i.e. the best fit.

The first 6 months rate of cognitive change in donepezil treated patients was strongly dependent of the baseline scores. The predicted mean rate of change with 95% confidence intervals showed more rapid improvement for the more severely affected patients with 30 and above on the ADAS cognitive subscale of 17 and below on the MMSE scale. This indicates a different slope and cognitive development compared to earlier studies of untreated patients.

For patients with at least 3 assessments each we predicted a longitudinal regression model for the dependent variable ADAS-cog score (330 patients, 1402 observation points), and for the variable MMSE score (390 patients, 1955 observation points) at different intervals. Several different and non-linear models were tested but these models showed the best fit.

The left figure shows a comparison between the treated patients’ predicted mean ADAS-cog scores from our regression model with 95% confidence intervals, and the mean predicted scores from the Stern equation calculated from untreated patients. Our model shows a favourable effect on cognition in donepezil treated patients with significant differences between the ADAS mean scores from 6 months and onwards (p<0.000). The right figure shows the mean predicted MMSE score with 95% confidence intervals from our multiple non-linear regression model calculated from donepezil treated patients. The shadow area shows the decline of 2-4 MMSE points/year based on historical untreated patients.